Tackling the Tuberculosis Epidemic in sub-Saharan Africa – unique opportunities arising from the second European Developing Countries Clinical Trials Partnership (EDCTP) programme 2015-2024

Alimuddin Zumla a, Eskild Petersen b, Thomas Nyirenda c, Jeremiah Chakaya d,*

a Center for Clinical Microbiology, Division of Infection and Immunity, University College London, NIHR Biomedical Research Centre, at UCHospital, London, United Kingdom
b Department of Infectious Diseases and Clinical Microbiology, Aarhus University Hospital Skejby, Aarhus, Denmark
c European Developing Countries Clinical trials Partnership, Cape Town, South Africa
d,Kenya Medical Research Institute (KEMRI), Nairobi, Kenya

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ABSTRACT

Tuberculosis (TB) today remains a global emergency affecting 9.0 million people globally. The African Region bears the highest global TB/HIV burden and over 50% of TB cases in SSA are co-infected with HIV. An estimated 1.5 million died from the TB globally in 2013. A large majority of the 360,000 HIV-positive TB cases who died were from sub-Saharan Africa. Research and development is an important pillar of the WHO post-2015 global TB strategy. Advances in development of diagnostics, drugs, host-directed therapies, and vaccines will require evaluation under field conditions through multi-centre clinical trials at different geographical locations. Thus it is critically important that these evaluations are fully supported by all African governments and the capacity, trained staff and infrastructure required to perform the research and evaluations is built and made available. This viewpoint article reviews the opportunities provided by recently launched second programme (2015-2024) of the European & Developing Countries Clinical Trials Partnership (EDCTP2) for tackling the TB epidemic in Africa through its magnanimous portfolio. The unique opportunities provided by EDCTP2 for leadership of scientific research in TB and other diseases fully devolving to Africa are also covered.

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Tuberculosis (TB) and HIV/AIDS remain two of the most common causes of death from an infectious disease worldwide1. The latest 2014 WHO global Annual Global TB report estimates that in 2013, there were 9.0 million people (3.3 million women and 500,000 children) who developed TB2 of which an estimated 1.2 million TB cases (14%) were in people living with HIV. TB imposes a huge burden on the already overstretched health services in sub-Saharan Africa (SSA). Although SSA has 12% of the world’s population it generated 29% of the 9 million TB cases and had 254,000 TB related deaths. SSA bears the highest global TB/HIV burden and over 50% of TB cases in SSA are co-infected with HIV2. An estimated 1.5 million died from TB globally in 2013, of which a large majority of the 360,000 HIV-positive TB cases who died were from sub-Saharan Africa.

The current WHO estimates on the global burden of TB2 may represent an underestimate of the actual burden since they are based mainly on calculations from reported TB case notification data and expert opinion about accuracy of reporting. In Africa the actual magnitude of the TB problem remains undefined due to poor laboratory and diagnostics infrastructure, case detection, recording and reporting systems. According to the WHO Report3 the first-ever national survey of the prevalence of TB disease in Nigeria was conducted in 2012 to estimate the prevalence of pulmonary TB among the general adult population. The data from it resulted in a substantial upward revision to WHO estimates of the country’s TB disease burden by 200% higher for incidence, 100% higher for prevalence and 400% higher for mortality4. Thus numbers of TB cases in SSA need to be defined more accurately since apart from identification of TB cases, there appears to be a large undiagnosed and sub-clinical load of TB as recently shown by studies in the inpatient paediatric5, adult6 and obstetrics wards7, at the University Teaching Hospital in Lusaka, Zambia, and from autopsy studies from Africa8.

An ominous increase is being seen globally in the number of new cases of Multi-Drug Resistant TB (MDR-TB)7,8, caused by

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Table 1
Components of the STOP TB Strategy [2]

1. Pursue high-quality DOTS expansion and enhancement
   a. Secure political commitment, with adequate and sustained financing
   b. Ensure early case detection, and diagnosis through quality-assured bacteriology
   c. Provide standardized treatment with supervision, and patient support
   d. Ensure effective drug supply and management
e. Monitor and evaluate performance and impact

2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations
   a. Scale up collaborative TB/HIV activities
   b. Scale up prevention and management of MDR-TB
   c. Address the needs of TB contacts, and of poor and vulnerable populations

3. Contribute to health system strengthening based on primary health care
   a. Help improve health policies, human resource development, financing, supplies, service delivery and information
   b. Strengthen infection control in health services, other congregate settings and households
   c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health
d. Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health

4. Engage all care providers
   a. Involve all public, voluntary, corporate and private providers through public–private mix approaches
   b. Promote use of the International Standards for Tuberculosis Care

5. Empower people with TB, and communities through partnership
   a. Pursue advocacy, communication and social mobilization
   b. Foster community participation in TB care, prevention and health promotion
   c. Promote use of the Patients’ Charter for Tuberculosis Care

6. Enable and promote research
   a. Conduct programme-based operational research
   b. Advocate for and participate in research to develop new diagnostics, drugs and vaccines

Mycobacterium tuberculosis (Mtbc) strains resistant to at least rifampicin and isoniazid, and of Extensively Drug-Resistant TB (XDR-TB), (resistance to rifampicin, isoniazid, plus any fluoroquinolone and at least one of the three injectable second line TB drugs: amikacin, kanamycin, capreomycin). There were an estimated 480,000 new cases of MDR-TB globally in 2013 [3]. These figures too are likely to be underestimated, especially in Africa due to a widespread lack of laboratory infrastructure and resources for drug-resistance testing. Molecular technologies such as GenoType MTBDRplus (Hain Lifescience, Germany), Xpert MTB/RIF (Cepheid, USA) are increasingly being incorporated into drug resistance surveys and laboratory services globally, including several SSA countries [4], and thus it is likely that MDR-TB numbers will be revised upward. Worryingly, the success rate of MDR-TB treatment was only 48% worldwide [5]. Weaknesses in health systems, lack of resources and ineffective treatment regimens coupled with other operational treatment challenges all contribute to the low cure rates.

The Global Plan to Stop TB 2011–2015 [10] set several targets [11] (Table 1) to curtail the co-epidemics of TB and HIV and the epidemic of MDR-TB. Key targets were that 100% of TB patients should know their HIV status, 100% of HIV-positive TB patients should receive antiretroviral therapy and that newly enrolled patients in HIV care programs with latent TB infection should receive preventive TB therapy with isoniazid. The main 2015 targets for MDR-TB were that all MDR-TB patients should be detected and treated with second-line TB treatment regimens, and the success rate should be >75%. To date none of these targets have been achieved in SSA [7].

Research and development is an important pillar of the WHO post-2015 global TB strategy [11]. The overall goal of the strategy is to end the global TB epidemic, with 2035 targets of a 95% reduction in TB deaths and a 90% reduction in TB incidence compared to 2015. Operational research should remain a priority [1,2] and ways to improve optimal delivery of TB and HIV health services, gaining patient confidence, acceptance and adherence to TB care and finding the missing 3 million cases of TB [14] must be found. New research and development into new diagnostic tests, new TB drugs, new treatment regimens which shorten duration of therapy, new regimens for MDR-TB, adjunct treatments, and new TB vaccines may play an important future role in achieving post-2015 global TB targets if any of them will prove to be of practical use for TB management at points of care. Whilst we await major scientific breakthroughs from the current research portfolio, it is of critical importance to note that there are important socio-economic factors coupled with poor housing and health services [12] that are main drivers of the global TB epidemic [13]. Unless these are seriously addressed by the global community and corrected, global TB control will be difficult to achieve and will take a long time. Meanwhile the huge TB load can be reduced significantly using currently available diagnostic tools and drug regimens if they are used and delivered optimally.

Several new TB diagnostics have become available over the past 5 years and some have undergone rapid evaluations in numerous studies [15]. Two new TB drugs, Bedaquiline and Delamanid, have emerged from the TB drug pipeline [16] and are being evaluated in several combinations in trials using adaptive designed for drug sensitive TB drug resistant TB and re-emerging drug resistant TB [18]. There are approximately 15 TB candidate vaccines being developed and several are undergoing phase 1, 2 and 3 evaluation [19]. All these new tools and interventions will need careful evaluation under field conditions in multi-centre clinical trials at different geographical locations. All new interventions and tools which show promise from initial evaluations should be viewed with cautious optimism as experience with the two Gamma interferon assays [20] and the Genexpert MTB/RIF assay [21] has shown. Both tests were rapidly and vigorously promoted due to the assumption they would revolutionize the TB diagnostic and management landscape. New technologies always perform well under controlled trial situations, and it is essential that they are evaluated under operational field conditions within health systems. The Xpert MTB/RIF Assay was seen and promoted as a game-changer in the TB diagnostic landscape but concerns remain with respect to implementation challenges for the lower levels of the health system, applicability as a point of care test, use in different epidemiological settings, advantage over time to treatment, effect on treatment outcome, and cost [7]. Furthermore new data which is generated without close engagement of local scientists, clinicians, end users and policy makers may hinder the implementation of research findings and recommendations into policy and practice. More importantly, individual research projects with limited grant funding, and dominance of basic science and clinical trials research in Africa by researchers from western country institutions [22] does not lead to effective development of local capacity, infrastructure and goodwill for research and infrastructure to be sustained long term.

Initial clinical trials of TB drugs and treatment regimens including short course chemotherapy were conducted in Africa in the 1950s by the UK Medical Research Council [21]. Since then there has been a dominance of ensuing TB clinical and epidemiological research activities in Africa by western countries with little involvement of African scientists [22]. As African countries gained independence and local universities were built, African scientists became increasingly empowered to take on the challenges of research on local health problems. The ‘annexed site’ and ‘parachute research’ colonial models of research which operated in Africa in the 20th century were challenged [23] and African led initiatives were initiated, which were successful in developing more equitable research and capacity development south–north partnerships [24]. The past two decades have seen a renaissance of
biomedical research, capacity development and training activities throughout SSA focused on malaria, HIV/AIDS, TB, parasitic infections and co-morbidities of communicable diseases with non-communicable diseases.

The establishment in 2003 of The European & Developing countries Clinical Trials Partnership (EDCTP)25,26 by the European Parliament and of the Council of the European Union was a major boost to these efforts for developing and sustaining local research, training and capacity development27–30. When the EDCTP was first launched in 2003 it was a partnership between 16 European countries, European Union and sub-Saharan Africa. EDCTP’s remit was to facilitate the progress of promising new technologies and products through the pipeline; conduct the necessary evaluation clinical trials in Africa; support ethics and regulatory components and promote collaboration with industry, product developers, other research funders and development cooperation agencies, and catalyze innovation toward the development of new or improved drugs, vaccines, microbicides and diagnostics for TB, HIV/AIDS and malaria. Despite pessimistic predications by armchair critics31,32 the mission and objectives of the EDCTP to become a game changer was applauded by African scientists33. Subsequently EDCTP successes and investments over the past decade may have surpassed that of any other scientific and capacity development funding agency or initiative in Africa27–33.

The TB-specific investments by EDCTP have focused on development of new TB diagnostics, drugs and vaccines and applications of existing diagnostic tools to expand clinical trials infrastructure in SSA33. EDCTP support has led to development of clinical trial partnerships between European and other international organizations with sub-Saharan African countries and mobilization of resources for establishment of clinical trials infrastructure including appropriate laboratory infrastructure. These sites are now being used for evaluation of several new TB diagnostics, TB drugs and drug regimens, and TB vaccines. The EDCTP-funded Pan African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA)34 consists of nine European universities and 11 African clinical trial centres. This consortium is evaluating several new TB drugs and TB treatment regimens. The Rapid Evaluation of Moxifloxacin in Tuberculosis (REMOXTB) trial35 was the first regulatory phase III clinical trial of a treatment-shortening regimen. The RIFAQUN Trial36 compared regimens that included weekly administration of high-dose rifapentine and moxifloxacin. Both trials showed that moxifloxacin–containing regimens were not effective in the African setting for shortening therapy to 4 months. Several EDCTP funded evaluations of new TB diagnostics showed that GeneXpert MTB/RIF Assay is useful in SSA settings to simplify patients’ access to early and accurate diagnosis and that it could be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV-associated TB37 and for more rapid proactive screening for subclinical TB and in paediatric, obstetrics and adult inpatient wards at tertiary care hospitals38,39. An EDCTP-funded trial of MVAB5 vaccine in HIV-infected adults in South Africa and Senegal is ongoing39.

The first programme of EDCTP ended in 2014. It made notable and significant investments in TB research and contributed to the establishment of state-of-the-art clinical and diagnostic laboratory infrastructure and training of a range of scientists and health personnel expediting TB related research40. So successful was the first EDCTP programme that on December 2nd 2014 there was a historic launch of the second programme (EDCTP2) in Cape Town under the auspices of the European Commission and the South African Department of Science and Technology27. EDCTP2 has changed its legal structure from a European Economic Interest Grouping to an Association under Dutch law enabling sub-Saharan African countries to also become full members of EDCTP40. This arrangement reflects EDCTP’s commitment to equal partnership built on joint ownership, leadership and trust with mutual benefit. Current EDCTP2 membership of the EDCTP Association now includes 13 European countries (Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, and United Kingdom) and 13 African countries (Cameroon, Republic of the Congo, The Gambia, Ghana, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda, Mali, Burkina Faso and Zambie).

EDCTP2 provides unique and extraordinary opportunities for facilitating and enhancing TB control efforts in SSA. By pooling resources, EDCTP increases coordination of national and regional research programs and reduces fragmentation and duplication. EDCTP2 investments will generate mutually beneficial collaborations among south-north institutions, simultaneously building capacity for conduct of large, multinational projects. Such an approach would enable large research projects that cannot be addressed by a single group and serve the large international footprint characteristic of such endeavors. With African governments as equal partners, close engagement of end-user communities and policy makers will allow national priorities for research to be taken forward and the results of research be translated into policy and practice. EDCTP2 will allow a cohesive program of multidisciplinary research to be undertaken to address some of the key questions that could impact on lowering the burden of TB disease in Africa and worldwide. This will also include high quality research that provides a step up change in our understanding of the optimization of health systems to deliver new or existing evidence-based interventions for the benefit of the peoples of Africa and beyond. EDCTP2 will also allow stimulation of dialogue about biomedical research and its impact on the public in a range of community and industry contexts; promote innovative partnerships between end users, community organizations and the cultural sector, and strengthen capacity to conduct public engagement with biomedical science and health research.

It is also anticipated that EDCTP2 partnerships and investments will lead to establishment and consolidation of an SSA wide resource of collaborating TB and TB/HIV centers, networks and expertise which will foster collaborations, stimulate, and expand basic, translational clinical and applied research, advancing scientific discovery. It is anticipated that more African research leaders will emerge and will lead independent self-perpetuating, African investigator-driven, long-lasting south-north research and training partnerships designed to address issues of local importance, coordinated through the utilization of common standards and practices. This will also ensure that research focuses on regional or national or continental relevant research questions, the answers to which will serve national and regional public health needs and priorities. This will no doubt enhance further development of novel health technologies, novel compounds and drugs from local resources and support multinational multi-disciplinary projects that combine clinical trials, capacity building and networking activities in partnership with European and other countries. The capacity built will also assist in regional and continental public health response to novel and emerging new infectious diseases threats40.

The overarching goal of the post-2015 WHO TB strategy is to end the global TB epidemic by 2035, with corresponding global targets for a 95% reduction in the number of TB deaths and a 90% reduction in the number of cases by 2035, compared with a baseline of 2015. Milestones for 2020, 2025 and 2030 are also included and that by 2020 no TB patients or their households experience catastrophic costs as a result of their disease. Achieving the proposed targets is based on three strategic pillars: integrated, patient-centered care and prevention; bold policies and supportive systems; and intensified research and innovation. As more African researchers take on leadership positions, it has become important
that other funding agencies consider aligning their research and capacity building investments in Africa with EDCTP to have a synergistic and multiplier effect. It is only through empowerment of the next generation of scientific leaders who will conduct the highest level of research that Africa will be able to generate local solutions to local health issues. The case in point here is that solutions for Africa’s TB problem should arise from African leadership of scientific research, fully engaged in redressing and resurrecting the imbalance underpinning scientific leadership and bringing equitable relationships with European scientists. ‘Holding hands together and moving forward in the fight against killer infectious diseases’ is the only way forward to achieve MDG targets. EDCTP2 investments into development of research and capacity in Africa through equitable north–south partnerships far surpasses that of any other and its laudable portfolio provides unique opportunities of leadership of scientific work fully devolving to Africa in TB/HIV and allow post-2015 TB targets to be achieved in SSA.

Author declarations: AZ serves on the Strategic Advisory Committee of the EDCTP. TN is EDCTP South-South Networking and Capacity Development Manager and TB focal person. All other authors declare no conflicts of interests.

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